REMARKS

Claims 1 to 46 are pending. Claims 1, 7, 13, 16, 17, 19, 29, 30, 33, 35, and 44 have been amended. Claims 11, 12, 14, 15, 23 to 26, 31, 32, and 39 to 43 have been canceled. New claims 47 to 54 have been added. Upon entry of the amendment, claims 1 to 10, 13, 16 to 22, 27 to 30, 33 to 38, and 44 to 54 will be pending.

Support for the amendment and new claims can be found throughout the specification and the original claims. Specifically, support for the amendment to claims 1, 7, 19, 30 and 35 can be found, for example, on page 9, line 4, to page 10, line 14, which indicates that a 6-mercaptopurine drug provides an active 6-mercaptopurine metabolite that has therapeutic efficacy such as 6-TG. Support for the amendment to claim 7 to recite levels of 6-mercaptopurine metabolites can be found in original dependent claims 11, 12, 14 and 15. Support for the amendment to claim 19 to recite levels of 6-mercaptopurine metabolites can be found in original dependent claims 23 to 26. Support for the amendment to claim 30 to recite levels of 6-thioguanine can be found in original dependent claims 31 and 32. Support for the amendment to claim 35 to recite levels of 6-mercaptopurine metabolites can be found in original dependent claims 39 to 43.

Support for new claims 47 to 51 can be found, for example, on page 9, line 4, to page 10, line 14, which indicates that a 6-mercaptopurine drug includes 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

Support for new claims 52 to 54 can be found, for example, on page 18, line 28, to page 19, line 25; page 22, lines 12-31; page 24, lines 3-29; and page 30, line 10, to page 33, line 21. Therefore, the amendment and new claims are full supported by the specification and do not add new matter. Accordingly, Applicants respectfully request entry of the amendment and new claims. Entry of the proposed amendments is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 1 to 46 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, is respectfully traversed. The Office Action states that, in claims 1, 7, 19, 30, 35 and 46, the term "drug" within the term "6-mercaptopurine drug treatment" is superfluous and can be deleted without changing the meaning of the term or claims. The Office Action also indicates that, in claims 1, 7, 19, 30, and 35, the "a" before "6-mercaptopurine drug" is superfluous.

Applicants respectfully maintain that claims 1, 7, 19, 30, 35, and 46 are clear and definite as written. As described in the previous response, the specification teaches that the term "6-mercaptopurine drug" refers to any drug that can be metabolized to an active 6-mercaptopurine metabolite that has therapeutic efficacy (page 9, lines 4-15) and further discloses

exemplary 6-mercaptopurine drugs, including 6-mercaptopurine, azathioprine, 6-methylmercaptopurine riboside and 6-thioguanine (page 9, lines 7-9 and 16-23). Accordingly, Applicants respectfully submit that the meaning of the term "6-mercaptopurine drug" is clear and definite. Nevertheless, in order to further prosecution, Applicants have amended claims 1, 7, 19, 30, 35, and 46 to delete the term "6-mercaptopurine drug."

Furthermore, the Office Action has requested on page 3, lines 14-15, that the claim be amended to indicate the name of active ingredients. Applicants have amended claims 1, 7, 19, 30, and 35 to indicate that the administered drug provides 6-thioguanine to the subject. Accordingly, Applicants respectfully submit that the claims are clear and definite and request that the Examiner remove this ground for rejecting the claims under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103(a)

The rejection of claims 1 to 46 under 35 U.S.C. § 103(a) as allegedly obvious over Sandborn, Scand. J. Gastroenterol. Suppl. 225:92-99 (1998) (the Sandborn reference) in view of Sandborn, U.S. Patent No. 5,733,915 (the Sandborn patent), and further in view of Berkow et al., The Merck Manual of Diagnosis and Therapy 16th Ed., Merck & Co., Rahway, NJ, pp. 328-330, pp. 826-828 and pp. 830-845 (1992), is respectfully traversed.

The Office Action states that the Sandborn reference is a review article describing the medicinal activity of azathioprine (AZA) and 6-mercaptopurine (6-MP) for treatment of Crohn's disease, inflammatory bowel disease, ulcerative colitis and related conditions. The Office Action also indicates that the Sandborn reference reports toxic effects of AZA and 6-MP administration, including pancreatitis, allergic reactions, drug hepatitis, and leukopenia. In regard to the Sandborn patent, the Office Action states that this reference describes the treatment of Crohn's disease by administration of azathioprine and 6-mercaptopurine and further specifies ranges for blood cell concentrations of 6-thioguanine and 6-methylmercaptopurine. The Berkow reference is cited as allegedly reporting that azathioprine and 6-mercaptopurine are effective in the treatment of Crohn's disease but that side effects such as pancreatitis and leukopenia are indicia of excessive immunosuppressive drug concentrations and must be avoided.

Applicants respectfully submit that the claimed methods are unobvious over the cited references. In particular, the Sandborn reference, alone or in combination with the Sandborn patent or Berkow et al., does not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity associated with drug treatment of an immune-mediated gastrointestinal disorder or non-IBD autoimmune disease by determining the levels of 6-mercaptopurine metabolites and whether the level of a particular 6-mercaptopurine metabolite is less than or greater than a specifically recited level of the 6-mercaptopurine metabolite.

Regarding claims 1 to 6

In regard to claim 1, as amended, and dependent claims 2 to 6, Applicants submit that the Sandborn reference does not teach or suggest a method for optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder by administering a drug to a subject having an immune-mediated gastrointestinal disorder, where the drug provides 6-thioguanine to the subject, and determining a level of 6-thioguanine (6-TG) in the subject, where a level of 6-TG less than about 230 pmol per $8x10^8$ red blood cells (RBCs) indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed methods obvious.

In regard to the Sandborn patent, this reference appears to describe the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine in Crohn's disease patients who received AZA intravenously for 36 hours followed by oral administration of AZA at 50 to 100 mg/day, or 100 to 150 mg/day if no clinical response was observed by 4 to 8 weeks (column 5, lines 7-23). The Sandborn patent does not teach or suggest the claimed methods of optimizing therapeutic efficacy associated with drug treatment by determining a level of 6-thioguanine, where a level less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of drug subsequently administered and where a level

greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered. At best, the Sandborn patent merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen.

Moreover, the Sandborn patent actually teaches away from the claimed invention. The Sandborn patent reports that "[C]linical response did not correlate with 6-TGN or 6-MeMP concentrations at the AZA dose studied" (column 7, lines 51-52)(emphasis added). The Sandborn patent further indicates that there was no significant correlation between the Crohn's disease activity index (CDAI) and the RBC 6-TGN or 6-MeMP concentrations at week 4, week 8, or week 16 (column 7, lines 61-67). Therefore, based on the description in the Sandborn patent, one skilled in the art would have had no motivation to determine a level of 6-TG and either increase or decrease the amount of drug subsequently administered if the 6-TG level is less than about 230 pmol/$8x10^8$ RBCs or greater than about 400 pmol/$8x10^8$ RBCs, respectively.

In regard to the specific levels of 6-MP metabolites described in the Sandborn patent, Applicants respectfully submit that the levels described in the Sandborn patent are significantly higher than the levels of 6-MP metabolites specifically recited in the claims. For example, the Sandborn patent states that 6-thioguanine nucleotide concentrations are preferably about 50 to 400 pmol/10^8 RBCs after intravenous therapy or about 50 to 500 pmol/10^8 RBCs after intravenous

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therapy while the patient is taking AZA orally (column 2, lines 49-54). In contrast, the predetermined minimal therapeutic level of 6-TG recited in claim 1 is about **230 pmol/8x10^8** RBCs. Upon conversion to the same factor, the levels described in the Sandborn patent of 50 to 400 pmol/10^8 RBCs equals **400 to 3200 pmol/8x10^8**; the levels of 50 to 500 pmol/10^8 RBCs equals **400 to 4000 pmol/8x10^8**. Thus, these levels are significantly higher than the predetermined minimal therapeutic 6-TG level of about 230 pmol/8x10^8 RBCs specifically recited in claim 1. In regard to a predetermined toxic level of 6-TG, the level recited in claim 1 of about 400 pmol/8x10^8 RBCs is actually the minimal level of 6-thioguanine nucleotide described in the Sandborn patent. Therefore, the Sandborn patent does not teach or suggest Applicants claimed methods reciting specific levels of 6-TG.

In regard to Berkow et al., the reference indicates that, in treating Crohn's disease with azathioprine or 6-mercaptopurine, side effects of allergy, pancreatitis or leukopenia "must be carefully watched for" (paragraph bridging pages 833-834). Therefore, Berkow merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored. Moreover, the reference fails to describe any relationship between 6-TG or 6-MMP levels and side effects. As such, Berkow et al. fails to teach or suggest the claimed methods of optimizing therapeutic efficacy and does not describe the specifically recited levels of 6-TG. Absent such a teaching or suggestion, Berkow et al. cannot render the claimed methods obvious. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG,

Applicants respectfully maintain that claims 1 to 6 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

Regarding claims 7 to 10, 13, and 16 to 18

In regard to claim 7, as amended, and dependent claims 8 to 10, 13, and 16 to 18, the Sandborn reference does not teach or suggest a method for reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder by administering a drug to a subject having an immune-mediated gastrointestinal disorder, where the drug provides 6-thioguanine to the subject; determining a level of 6-TG and 6-methyl-mercaptopurine (6-MMP) in the subject, where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs or a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered to the subject, thereby reducing toxicity associated with drug treatment of the immune-mediated gastrointestinal disorder. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed invention obvious.

In regard to the Sandborn patent, this reference, as discussed above, merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen. However, the Sandborn patent does not teach or suggest the claimed methods of reducing toxicity by determining a level of 6-TG or 6-MMP, where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs or a level of 6-MMP

greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered.

In regard to the predetermined toxic level of 6-TG, as described above, the Sandborn patent actually teaches away from the claimed invention by describing a minimal level of 6-TG, 400 pmol/$8x10^8$ RBCs, that is the predetermined toxic level of 6-TG recited in claim 7. The Sandborn patent also teaches away from the claimed invention in regard to 6-MMP levels. Specifically, the Sandborn patent indicates that 6-methylmercaptopurine "is preferably about 1000 to 7000 pmol/10^8 red blood cells" (column 2, lines 54-57), which equals **8000 to 56,000 pmol/$8x10^8$ RBCs**. In contrast, the predetermined toxic level of 6-MMP recited in claim 7 is about **7000 pmol/$8x10^8$ RBCs**. Thus, the preferred level of 6-MMP described in the Sandborn patent is higher than the predetermined toxic level of 6-MMP recited in claim 7. Thus, the Sandborn patent teaches away from the predetermined 6-TG toxic level of 400 pmol/$8x10^8$ RBCs and the predetermined 6-MMP toxic level of 7000 pmol/$8x10^8$ RBCs specifically recited in claim 7 and cannot render the claimed methods obvious.

In regard to Berkow et al., this reference, as described above, merely states that treatment with azathioprine or 6-mercaptopurine may have side effects that should be monitored but fails to describe any relationship between 6-TG or 6-MMP levels and side effects or the specifically recited levels of 6-TG or 6-MMP. As such, Berkow et al. does not teach or suggest the claimed method of reducing toxicity by determining a level of 6-TG and 6-MMP, where a level of 6-TG greater than about

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400 pmol per $8x10^8$ RBCs or a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG and 6-MMP, Applicants respectfully maintain that claims 7 to 10, 13, and 16 to 18 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

Regarding claims 19 to 22 and 27 to 29

In regard to claim 19, as amended, and dependent claims 20 to 22 and 27 to 29, the Sandborn reference does not teach or suggest a method for optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder by administering a drug to a subject having an immune-mediated gastrointestinal disorder, where the drug provides 6-thioguanine to the subject; and determining a level of 6-TG and 6-MMP in the subject, where a level of 6-TG less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of drug subsequently administered to the subject, where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered to the subject, and where a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered to the subject. Absent such a teaching or suggestion, the Sandborn reference cannot render the claimed methods obvious.

In regard to the Sandborn patent, this reference, as discussed above, merely describes the levels of 6-thioguanine nucleotide and 6-methylmercaptopurine associated with a specific AZA treatment regimen. However, the Sandborn patent does not teach or suggest the claimed methods of optimizing therapeutic efficacy and reducing toxicity by determining a level of a 6-TG and 6-MMP or the specifically recited levels of 6-TG and 6-MMP. Furthermore, as described above, Sandborn actually teaches away from the claimed methods in that the preferred level of 6-TG described in Sandborn (400 to 4000 pmol/$8x10^8$) is significantly higher than the minimal therapeutic level of 6-TG of about 230 pmol/$8x10^8$ RBCs specifically recited in claim 19. Moreover, the Sandborn patent also teaches away from the claimed invention by describing a minimal level of 6-TG, 400 pmol/$8x10^8$ RBCs, that is the predetermined toxic level of 6-TG specifically recited in claim 19. In addition, the Sandborn patent further teaches away from the claimed methods in that the preferred level of 6-MMP (8000 to 56,000 pmol/$8x10^8$ RBCs) described in the Sandborn patent is higher than the predetermined toxic level of 6-MMP of 7000 pmol/$8x10^8$ RBCs specifically recited in claim 19. Accordingly, Applicants maintain that the Sandborn patent cannot render the claimed methods obvious.

In regard to Berkow et al., this reference, as described above, does not teach or suggest the claimed method of optimizing therapeutic efficacy and reducing toxicity by determining a level of a 6-TG and 6-MMP, where a level of 6-TG less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of drug subsequently administered to the

subject, where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered to the subject, and where a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered to the subject. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG and 6-MMP, Applicants respectfully maintain that claims 19 to 22 and 27 to 29 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

Regarding claims 30 and 34

In regard to claim 30, as amended, and dependent claim 34, neither the Sandborn reference, the Sandborn patent, nor Berkow et al., for the reasons described above, teach or suggest a method of optimizing therapeutic efficacy of treatment of non-IBD autoimmune disease by administering a drug to a subject, where the drug provides 6-thioguanine to the subject, and determining a level of 6-TG, where a level less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of drug subsequently administered and where a level greater than about 400 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of drug subsequently administered. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG, Applicants respectfully maintain that claims 30 and 34 would not have been obvious in

view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

Regarding claims 35 to 38, 44 and 45

In regard to claim 35, as amended, and dependent claims 36 to 38, 44 and 45, neither the Sandborn reference, the Sandborn patent, nor Berkow et al., for the reasons described above, teach or suggest a method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder by administering a drug to a subject having the immune-mediated gastrointestinal disorder, where the drug provides 6-thioguanine to the subject; and determining a level of 6-TG and 6-MMP in the subject, where a level of 6-TG less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of the drug subsequently administered to the subject, and where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs or a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of the drug subsequently administered to the subject. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG, Applicants respectfully maintain that claims 35 to 38, 44 and 45 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

Regarding new claims 52 to 54

In regard to new claim 52, and dependent claims 53 and 54, Applicants respectfully submit that, for the reasons described above, neither of the Sandborn reference, the Sandborn patent, nor Berkow et al. teach or suggest a method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease by administering a drug to a subject having the non-IBD autoimmune disease, where the drug provides 6-thioguanine to the subject; and determining a level of 6-TG and 6-MMP in the subject having the non-IBD autoimmune disease, where a level of 6-TG less than about 230 pmol per $8x10^8$ RBCs indicates a need to increase the amount of the drug subsequently administered to the subject and where a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs or a level of 6-MMP greater than about 7000 pmol per $8x10^8$ RBCs indicates a need to decrease the amount of the drug subsequently administered to the subject. Since none of the cited references teach or suggest Applicant's claimed methods reciting specific levels of 6-TG and 6-MMP, Applicants respectfully maintain that new claims 52 to 54 would not have been obvious in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow et al.

In summary, Applicants respectfully submit that the cited references do not teach or suggest the claimed methods of optimizing therapeutic efficacy and/or reducing toxicity of an immune-mediated gastrointestinal disorder or non-IBD autoimmune disease by determining a level of 6-TG or 6-MMP and increasing or decreasing the amount of drug subsequently administered if the

level is below a specifically recited level of 6-TG or above a specifically recited level of 6-TG or 6-MMP. Therefore, Applicants respectfully maintain that the claimed methods would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of the Sandborn reference, alone or in combination with any of the Sandborn patent or Berkow. Accordingly, Applicants respectfully request that the Examiner remove this ground for rejecting the claims under 35 U.S.C. § 103(a).

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Date

Deborah L. Cadena
Registration No. 44,048
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
Suite 700
San Diego, California 92122
USPTO CUSTOMER NO. 23601